

Claims

1. A process for the preparation of a substantially pure amorphous 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A, wherein the procedure comprises the steps of:

a) dissolving 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A material in

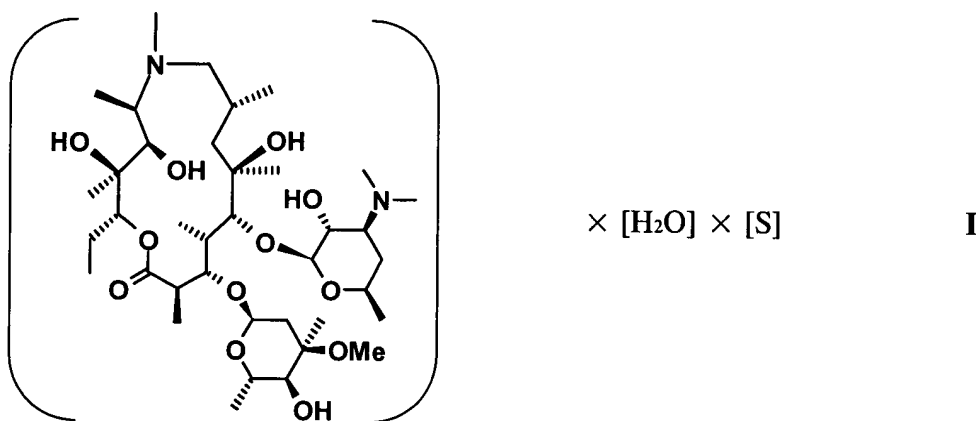
(1) an organic solvent that is water-miscible or water-immiscible,

(2) a mixture of organic solvents,

(3) a mixture of organic solvents and water, or

(4) a mixture of water and at least one inorganic or organic acid;

b) crystallizing an orthorhombic isostructural pseudopolymorph of 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A of the general Formula I



wherein S is a water-miscible or water-immiscible organic solvent,

the pseudopolymorph being characterized by the orthorhombic space group $P2_12_12_1$ and average unit cell parameters comprising:

crystal axis lengths of $a = 8.2$ to 9.7 Å, $b = 11.5$ to 13.5 Å, and $c = 44.5$ to 47.0 Å, and

angles between the crystal axes of $\alpha = \beta = \gamma = 90^\circ$, from the solution thus prepared;

c) isolating the orthorhombic isostructural pseudopolymorph of the general Formula I;
and

28 d) converting the orthorhombic isostructural pseudopolymorph of 9-deoxo-9a-aza-9a-
29 methyl-9a-homoerythromycin A of the general Formula I to a substantially pure
30 amorphous 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A.
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1 2. The process of claim 1, wherein the 9-deoxo-9a-aza-9a-methyl-9a-
2 homoerythromycin A material dissolved in step (a) is (i) a crystalline 9-deoxo-9a-aza-9a-
3 methyl-9a-homoerythromycin A in crude or purified form, (ii) an amorphous 9-deoxo-9a-aza-
4 9a-methyl-9a-homoerythromycin A in crude or purified form, (iii) solvates or hydrates of 9-
5 deoxo-9a-aza-9a-methyl-9a-homoerythromycin A, whether in crude or purified form, or (iv) a
6 native solution of 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A formed during the last
7 step of its syntheses from any one of its last intermediates.

1 3. The process of claim 2, wherein the 9-deoxo-9a-aza-9a-methyl-9a-
2 homoerythromycin A utilized to prepare a substantially pure amorphous 9-deoxo-9a-aza-9a-
3 methyl-9a-homoerythromycin A, dissolved in step (a) is a crude 9-deoxo-9a-aza-9a-methyl-9a-
4 homoerythromycin A in any of its known forms and having a purity less than the
5 pharmaceutically acceptable purity.

1 4. The process of claim 2, wherein the native solution of 9-deoxo-9a-aza-9a-
2 methyl-9a-homoerythromycin A used for preparing a substantially pure amorphous 9-deoxo-9a-
3 aza-9a-methyl-9a-homoerythromycin A, in the solvent dissolved in step (a) is a solution of 9-
4 deoxo-9a-aza-9a-methyl-9a-homoerythromycin A formed in the native solvent during the last
5 step of its syntheses from any one of its last intermediates.

1 5. The process of claim 2, wherein the native solution of 9-deoxo-9a-aza-9a-
2 methyl-9a-homoerythromycin A used for preparing substantially pure amorphous 9-deoxo-9a-
3 aza-9a-methyl-9a-homoerythromycin A dissolved in step (a) is a solution of 9-deoxo-9a-aza-9a-
4 methyl-9a-homoerythromycin A, formed in the native solvent during the last step of its
5 syntheses from 9-deoxo-9a-aza-9a-homoerythromycin A as its last intermediate.

1 6. The process of claim 2, wherein the 9-deoxo-9a-aza-9a-methyl-9a-
2 homoerythromycin A dissolved in step (a) is in the form of a dispersion of 9-deoxo-9a-aza-9a-
3 methyl-9a-homoerythromycin A and the 9-deoxo-9a-aza-9a-homoerythromycin A intermediate
4 in a native solvent used in the last step of a synthesis of crude 9-deoxo-9a-aza-9a-methyl-9a-
5 homoerythromycin A.

1 7. The process of claim 4, wherein the native solvent in the native solution is
2 selected from the group consisting of haloalkanes having 1 or 2 carbon atoms, esters of acetic
3 acid with a C₂-C₄ lower alkyl group, monohydroxyl C₂-C₄ alkanols, C₁-C₄ ketones, linear or
4 cyclic ethers, aromatic or substituted aromatic compounds, and mixtures thereof.

1 8. The process of claim 2, wherein the 9-deoxo-9a-aza-9a-methyl-9a-
2 homoerythromycin A dissolved in step (a) is amorphous 9-deoxo-9a-aza-9a-methyl-9a-
3 homoerythromycin A; a crystalline anhydrous, monohydrate, dihydrate or solvate of 9-deoxo-
4 9a-aza-9a-methyl-9a-homoerythromycin A; or an orthorhombic isostructural pseudopolymorph
5 of 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A of Formula I.

1 9. The process of claim 2, wherein the 9-deoxo-9a-aza-9a-methyl-9a-
2 homoerythromycin A dissolved in step (a) is of pharmaceutically acceptable purity.

1 10. The process of claim 1, wherein step (a) is conducted at a temperature of
2 from about 30°C to about 100°C.

1 11. The process of claim 1, wherein the organic solvent in which the 9-deoxo-
2 9a-aza-9a-methyl-9a-homoerythromycin A material is dissolved in step (a) is selected from the
3 group consisting of linear or branched C₁-C₅ alkanes, C₅-C₈ cycloalkanes, linear or branched
4 C₁-C₆ alkanols, C₅-C₈ cycloalkanols, arylalkanols, C₂-C₄ diols, triols, C₁-C₄ ethers, C₃-C₅
5 ketones, C₁-C₄ alkyl esters of C₁-C₄ alkanolic and hydroxyalkanoic acids, amides, ureas, C₂-C₄
6 nitriles, sulfoxides, sulfones, heterocyclic amines, lactams, and mixtures thereof.

1 12. The process of claim 1, wherein the inorganic of acid is selected from the
2 group consisting of hydrochloric acid, sulfuric (VI) acid, sulfuric (IV) acid, and mixtures
3 thereof.

1 13. The process of claim 1, wherein the organic acid is selected from the group
2 consisting of formic acid, acetic acid, propionic acid, citric acid, tartaric acid, maleic acid,
3 oxalic acid, chloroacetic acid, benzoic acid, methanesulfonic, *p*-toluenesulfonic acid, and
4 mixtures thereof.

1 14. The process of claim 1, wherein the orthorhombic isostructural
2 pseudopolymorph of 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A is crystallized in step
3 (b) by controlled cooling of the solution containing the 9-deoxo-9a-aza-9a-methyl-9a-
4 homoerythromycin A at temperatures of from about 80°C to about -10°C.

1 15. The process of claim 1, wherein the orthorhombic isostructural
2 pseudopolymorph of 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A is crystallized in step
3 (b) isothermally at temperatures of from about 25°C to about 60°C, by standing or mixing the
4 solution formed in step (a) in a water-miscible or water-immiscible organic solvent at said
5 isothermal conditions.

1 16. The process of claim 1, wherein the orthorhombic isostructural
2 pseudopolymorph of 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A is crystallized in step
3 (b) isothermally at a temperature of about 25°C to about 60°C by saturating the solution
4 formed in step (a) in a water-miscible or water-immiscible organic solvent with an organic
5 counter-solvent until the solution becomes slightly turbid.

1 17. The process of claim 16, wherein the organic counter-solvent is water.

1 18. The process of claim 1, wherein the orthorhombic isostructural
2 pseudopolymorph of 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A is crystallized in step

3 (b) by neutralizing the aqueous acidic solution of 9-deoxo-9a-aza-9a-methyl-9a-
4 homoerythromycin A formed in step (a) at temperatures of about 80°C to about -10°C.

1 19. The process of claim 1, wherein the orthorhombic isostructural
2 pseudopolymorph of general Formula I is crystallized in step (b) by neutralizing an acidic
3 solution of 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A material from step (a) with one
4 or more inorganic or organic base.

1 20. The process of claim 18, wherein the inorganic base is a alkali or alkali-
2 earth metal hydroxide, oxide or carbonate, or an ammonia solution.

1 21. The process of claim 19, wherein the organic base is an organic amine.

1 22. The process of claim 21, wherein the organic amine is selected from the
2 group consisting of trimethylamine, triethylamine, piperidine, 3-methylpyridine, piperazine,
3 triethanolamine, and ethylene diamine.

1 23. The process of claim 19, wherein the organic base is a quaternary organic
2 hydroxide.

1 24. The process of claim 23, wherein the quaternary organic hydroxide is
2 selected from the group consisting of tetramethyl ammonium hydroxide, tetraethyl ammonium
3 hydroxide, and tetrabutyl ammonium hydroxide.

1 25. The process according to claim 1, wherein the orthorhombic isostructural
2 pseudopolymorph of 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A of Formula I is added
3 to the solution in step (b) in an amount of from about 0.01 to about 5.0 wt. % based on the
4 amount of the starting 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A, to seed
5 crystallization of the orthorhombic isostructural pseudopolymorph of the general Formula I
6 therein.

1 26. The process of claim 1, wherein the orthorhombic isostructural
2 pseudopolymorph of 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A of Formula I is
3 isolated in step (c) by:

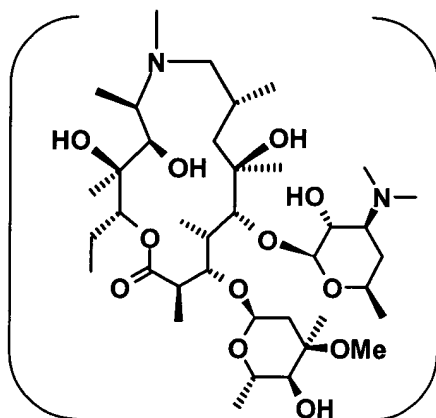
- 4 (i) separating the pseudopolymorph from the solution formed in step (a);
5 (ii) washing the obtained product with solvents (1), (2) or (3) used in step
6 (a), at temperatures of from about -10°C to about 40°C; and
7 (iii) drying the washed product under atmospheric pressure at temperatures of
8 from about 20°C to about 80°C, or under reduced pressures of from
9 about 2 kPa to about 80 kPa.

1 27. The process of claim 1, wherein the orthorhombic isostructural
2 pseudopolymorph of Formula I is transformed in step (d) to a substantially pure stable
3 amorphous 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A by lyophilizing or further
4 drying the orthorhombic isostructural pseudopolymorph at reduced pressures from about 0.01
5 kPa to about 80 kPa and temperatures of from about -100°C to about 100°C.

1 28. The process of claim 1, wherein the substantially pure amorphous 9-deoxo-
2 9a-aza-9a-methyl-9a-homoerythromycin A prepared in step (d) is characterized by the non-
3 existence of isolated peaks in powder diffractogram, by a water content of from about 1.5 to
4 about 2.5%, a granular habit, a specific dissolution profile as well as a specific intrinsic
5 dissolution rate (IDR) at 37°C.

1 29. The substantially pure orthorhombic isostructural pseudopolymorph of
2 Formula I, prepared by the process of claim 1.

1 30. A substantially pure orthorhombic isostructural pseudopolymorph of 9-
2 deoxo-9a-aza-9a-methyl-9a-homoerythromycin A of the general formula I
3
4



wherein S represents a water-miscible or water-immiscible organic solvent, characterized by the orthorhombic space group $P2_12_12_1$, and having average unit cell parameters of

$$a = 8.2 \text{ to } 9.7 \text{ \AA},$$

$$b = 11.5 \text{ to } 13.5 \text{ \AA},$$

$$c = 44.5 \text{ to } 47.0 \text{ \AA}, \alpha = \beta = \gamma = 90^\circ,$$

wherein a, b and c represent the crystal axes lengths, and α , β and γ represent the angles between the crystal axes.

31. The substantially pure orthorhombic isostructural pseudopolymorph of 9-deoxy-9a-aza-9a-methyl-9a-homoerythromycin A of claim 29 selected from the group of pseudopolymorphs (Ia) – (Id) set forth below, wherein S in Formula I and the average unit cell parameters, i.e. the crystal axes lengths a, b and c, and angles α , β and γ between the crystal axes of the crystal structure are:

(Ia) S = 1,4-dioxane, and at 22°C:

$$a = 8.8290(20) \text{ \AA},$$

$$b = 12.167(2) \text{ \AA},$$

$$c = 45.853(8) \text{ \AA}, \text{ and}$$

$$\alpha = \beta = \gamma = 90^\circ,$$

(Ib) S = *tert*-butanol and, at -173°C:

a = 8.84240(10) Å,
b = 11.91730(10) Å,
c = 45.9493(6) Å, and
 $\alpha = \beta = \gamma = 90^\circ$

(Ic) S = methyl *tert*-butyl ether and, at 22°C:

a = 8.92080(10) Å,
b = 12.34770(10) Å,
c = 45.71900(10) Å, and
 $\alpha = \beta = \gamma = 90^\circ$,

(Id) S = cyclohexane and, at 22°C:

a = 8.8573(23) Å,
b = 12.520(7) Å,
c = 45.624(11) Å, and
 $\alpha = \beta = \gamma = 90^\circ$.

32. Substantially pure amorphous 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A prepared by the process of Claim 1.

33. The substantially pure amorphous 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A prepared by the process of Claim 1, characterized by the non-existence of isolated peaks in a powder diffractogram, a water content from about 1.5 to about 2.5 %, a granular habit, a specific dissolution profile as well as a specific intrinsic dissolution rate (IDR) at 37°C.

34. A pharmaceutical composition comprising substantially pure amorphous 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A prepared by the process of claim 1, and one or more pharmaceutically acceptable excipients.

1 35. A pharmaceutical composition for oral, rectal, parenteral, transdermal,
2 buccal, nasal, sublingual, subcutaneous or intravenous application, comprising substantially
3 pure amorphous 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A, prepared by the process
4 of claim 1, and one or more pharmaceutically acceptable excipients.

5 36. A method for treating bacterial and protozoal infections, and inflammation-
6 related diseases in humans and animals, comprising administering to a human or animal in
7 need thereof the pharmaceutical composition of claim 34.